

**STUDIES ON SIDE EFFECT PROFILE OF TREATED
HYPERTENSIVES ON SELECTED PHARMACOTHERAPY**

by

DR MARINA ISMAIL

**Dissertation Submitted In Partial Fulfilment Of The
Requirements For The Degree Of Master Of Medicine
(Internal Medicine)**

**UNIVERSITI SAINS MALAYSIA
2001**

ACKNOWLEDGEMENTS

I would like to thank my supervisors, Associate Professor (Dr) Rusli Ismail and Professor (Dr) Wan Mohamad Wan Bebakar for their valuable advice and guidance for the preparation of this dissertation. Their help and guidance has made this study possible and has enabled me to be more familiar in designing and carrying out research.

My special gratitude for Ms. Teh Lay Kek from Department of Pharmacy, University Malaya for her helped in preparing the questionnaires on quality of life assessment.

Not to forget, my husband En. Zakaria Hamid for his continued support and help in preparing the research. Also to my children, Mohd. Amir Ashraf, Mohd. Amir Afiq and Nur Ain Shafiqah for their understanding and cooperation during the period of this study.

Lastly, I would like to express my heartfelt gratitude to all the volunteers who have participated in this study and hope that the results of this study will contribute towards improving the management of hypertension.

This dissertation has got many weaknesses which was highlighted by examiners and has been discussed in the viva voce. I have highlighted the weaknesses and have written an extra chapter to outline these weaknesses. I am also grateful to the examiners for pointing out the weaknesses and gave the beneficial comments to prepare this chapter.

Table of Content

Acknowledgements	ii
Table of content	iv
List of Tables	vi
List of Illustrations	vii

Abstract

Bahasa Malaysia	viii
English	xii

CHAPTER

Chapter 1: Introduction

1.0	Introduction	1
1.1	Beta blocker as an antihypertensive drug	10
1.2	Health related quality of life	17

Chapter 2 : Objectives

2.	Objectives	23
----	------------	----

Chapter 3 : Method

3.1	Patients selection	24
3.1.1	Inclusion criteria	24
3.1.2	Exclusion criteria	25
3.2	Study Design and clinical methods	25
3.2.1	Laboratory investigations	26
3.2.2	Follow-up visits	29

3.2.3	Criteria for diagnosing hypertension	29
3.3	Statistical analysis	29

Chapter 4 : Results

4.1	Demography	31
4.2	Hypertension related complications	39
4.3	Clinical results	41
4.4	Biochemical results	47
4.5	Adverse effects	51
4.6	Life satisfactions	62

Chapter 5 : Discussion	65
-------------------------------	-----------

Chapter 6 : Conclusion	79
-------------------------------	-----------

Chapter 7 : Critics and limitation	80
---	-----------

References	87
-------------------	-----------

Appendix

Appendix I	95
Appendix II	96

List of Tables

Table 1	General measures of the quality of life.
Table 4.1.0	Concurrent Antihypertensive drug Received by Patients.
Table 4.1.1	Racial Distribution Among Study Groups.
Table 4.1.2	Sexual Distribution Among Study Groups.
Table 4.1.3	Physical Characteristics of Study Patients.
Table 4.2.0	Number of Patients Who Reported Stroke/TIA According to Treatment Groups.
Table 4.3.0	Average Blood Pressures and Pulse Rates According to Study Groups.
Table 4.4.0	Results of Laboratory Examination Treatment Groups.
Table 4.5.0	Ranking of Adverse Events According to Drug Groups.
Table 4.6.0	Life Satisfaction of the Study Patients.

List of Illustration.

Figure 1.	Study Design.
Figure 4.1.0	Age Distribution Among Study Patients.
Figure 4.3.0	Systolic Blood Pressure Distribution in Study Patients.
Figure 4.3.1	Diastolic Blood Pressure in Study Patients.
Figure 4.3.2	Percentage of Patients who achieved blood pressure control.
Figure 4.4.0	Serum ALP According to Drug Groups.
Figure 4.4.1	Serum AST According to Drug Groups.
Figure 4.5.0	Adverse Symptoms Reported By All Patients.
Figure 4.5.1	Average Frequency Scores Adverse Symptoms in All Patients.
Figure 4.5.2	Severity of Adverse Events Reported.
Figure 4.5.3	Occurrence of Adverse Events According to Drug Groups.

ABSTRACT

ABSTRAK

Kajian kesan sampingan terhadap penyakit darah tinggi berdasarkan ubat-ubatan terpilih.

Latarbelakang: Penyakit darah tinggi merupakan sejenis penyakit yang memberikan implikasi yang besar kepada kesihatan seseorang pesakit. Rawatan penyakit ini adalah penting bagi mengurangkan kadar komplikasi dan kematian. Kawalan terhadap tekanan darah melalui penggunaan ubat-ubatan yang dapat bertindak balas dengan baik, dos yang bersesuaian dan kos yang rendah adalah diperlukan. Disamping itu, penggunaan ubat yang paling baik dan mempunyai kesan sampingan yang paling sedikit perlu diamalkan. Ini adalah penting bagi memastikan penggunaan ubat dapat diambil secara berterusan dan kualiti kehidupan pesakit dapat dipertingkatkan. Di Hospital USM, metoprolol digunakan secara meluas. Metabolismanya dipengaruhi oleh kepelbagaian debrisoquine-hydroxylase yang mempunyai perbezaan yang ketara antara sesebuah bangsa atau etnik. Kebanyakan kesan sampingan mungkin dipengaruhi oleh paras ubat yang berlebihan di dalam darah yang diakibatkan oleh kurangnya metabolisme dalam tubuh seseorang. Oleh yang demikian, objektif kajian ini adalah untuk mengkaji penggunaan metoprolol dan kesan sampingan dalam merawat penyakit darah tinggi. Kajian ini juga dibuat bagi menentukan samada pesakit yang mendapat kesan sampingan mengalami kualiti kehidupan yang tidak memuaskan. Sebagai perbandingan, kajian terhadap pesakit darah tinggi yang

mendapat rawatan dengan enalapril atau kombinasi enalapril dan metoprolol dilakukan.

Kaedah: Dua ratus pesakit darah tinggi yang dirawat dengan metoprolol dan/atau enalapril di Klinik Pakar Perubatan, HUSM telah dipilih. Pesakit-pesakit yang telah disahkan menghidap penyakit kencing manis, penyakit jantung koronari, kegagalan buah pinggang yang kronik, kegagalan jantung penyakit-penyakit kronik yang lain dikecualikan. Pesakit yang mengidap penyakit seperti barah telah dikecualikan dari kajian kerana dikhuatiri akan mengganggu penyiasatan. Demografi pesakit direkodkan pada lawatan pertama dan seterusnya pada lawatan ulangan. Kualiti kehidupan pesakit dikaji berdasarkan borang soal selidik.

Keputusan: Dua ratus pesakit yang dirawat dengan metoprolol dan/atau enalapril telah dipilih. Kebanyakan pesakit di dalam kajian ini adalah daripada bangsa Melayu. Purata umur pesakit adalah 53.4 tahun dan separuh daripada mereka adalah lelaki. 77 pesakit darah tinggi mendapat rawatan dengan metoprolol, 99 orang pesakit dirawat dengan enalapril dan 24 orang pesakit mendapat rawatan kombinasi metoprolol-enalapril. 48% pesakit mempunyai purata tekanan darah sistolik 140 mmHg atau kurang dan 28% mempunyai purata tekanan darah diastolik 80 mmHg atau kurang. 42% pesakit metoprolol, 43% pesakit enalapril dan 40% pesakit yang mendapat rawatan

kombinasi metoprolol-enalapril mempunyai purata tekanan darah sistolik ≤ 140 mmHg dan purata tekanan darah diastolik ≤ 90 mmHg.

Tidak ada perbezaan statistik yang ketara dalam penyiasatan biokemikal darah pesakit dalam kajian ini. Kebanyakan kesan sampingan dilaporkan oleh pesakit di dalam kumpulan yang menerima rawatan kombinasi metoprolol-enalapril.

Walaupun, sebahagian kesan sampingan yang dilaporkan lebih ketara di dalam pesakit yang dirawat dengan metoprolol. Ini meliputi bradikardia (gerakan nadi yang perlahan), sejuk bahagian hujung kaki dan tangan, kencing pada waktu malam dan berdebar-debar. Hampir kesemua pesakit melaporkan bahawa mereka berpuashati dengan kualiti kehidupan. Sebahagian kecil yang tidak berpuashati dengan kualiti kehidupan datangnya dari kumpulan yang mendapat rawatan metoprolol.

Kesimpulan: Kajian ini menunjukkan bahawa tidak sampai separuh daripada pesakit kami yang menerima rawatan samada metoprolol, enalapril atau kombinasi metoprolol-enalapril mencapai tahap kawalan tekanan darah yang memuaskan. Kebanyakannya melaporkan bahawa mereka mendapat kesan sampingan daripada rawatan yang diberikan. Kesan sampingan ini berkait rapat dengan dos ubat yang diberi terutamanya pesakit yang mendapat rawatan metoprolol. Ini mungkin menyebabkan kurangnya penggunaan ubat secara berterusan menyebabkan tekanan darah tinggi tidak dapat dikawal secara berkesan. Ini juga mungkin dipengaruhi oleh kurangnya kebolehan untuk

metabolisma metoprolol terhadap pesakit yang mempunyai kepelbagaian genetik debrisoquine-hydroxylasde. Oleh itu, kajian lanjut berkenaan dengan kepelbagaian genetik dan fenotaip akan memberikan jawapan kepada masalah di atas.

ABSTRACT

Background: Hypertension is a major public health problem because of its consequences. Its treatment is crucial and goals include to decrease morbidity and mortality associated with hypertension by decreasing blood pressure using drugs that have good tolerance, dosing convenience and low cost. As many antihypertensives are now available, it is important to choose the most appropriate drug in terms of efficacy and with least side effect in order to improve compliance and the patient's quality of life. In HUSM, metoprolol is a widely used. Its metabolism is mediated by the polymorphic debrisoquine-hydroxylase that exhibits large inter ethnic difference. As most of its adverse reactions could be due to excessive plasma concentrations, its use among our local population may therefore be associated with adverse effects due to reduced capacity of the local population to metabolise the drug. The objectives of this study were therefore to investigate the use of metoprolol in the treatment of hypertension in relation to the incidence of adverse drug reactions it caused. We would also determine whether patients who experienced adverse reactions suffered reduced quality of life. As controls, we used patients who received enalapril or enalapril combined with metoprolol in the treatment of their hypertension.

Method: Two hundred hypertensive patients treated with metoprolol and/or enalapril at the Hypertensive Clinic, HUSM were recruited. Those excluded were patients diagnosed to have diabetes mellitus, ischaemic heart disease, chronic renal failure, congestive cardiac failure and those who suffered from other chronic diseases for example malignancy, which may interfere with the proper use of the investigation instrument. Patients' demography were recorded and biochemical profile were taken. The clinical observation were recorded during the first visit and at follow up. Their quality of life assessment were assessed using questionnaire.

Result: Two hundred hypertensive patients treated with metoprolol and/on enalapril were enrolled. The majority were Malays. Their age averaged 53.4 years and half were males. Seventy-seven received metoprolol as their primary antihypertensive drug, 99 were on enalapril and 24 were on combination metoprolol-enalapril therapies. 48% had systolic blood pressure (SBP) that averaged 140 mmHg or below and 28% had diastolic blood pressure (DBP) that averaged 80 mmHg or below. 42% metoprolol patients, 43% enalapril patients and 40% combined-therapy patients had blood pressure control (average SBP \leq 140 mmHg and average DBP \leq 90 mmHg) $p=0.979$.

No statistical significant difference in blood chemistries occurred among the study groups. Adverse events were reported frequently by the patients and were most frequently reported by patients on combination-therapy. Some adverse effects were more significant with patients on metoprolol. These included bradycardia, cold extremities, nocturia, and palpitation. Almost all however reported that they were satisfied with their lives but those who said that they were not satisfied came from the metoprolol group.

Conclusion: Our study showed that less than half of our patients treated with either metoprolol, enalapril or metoprolol-enalapril combination achieved satisfactory blood pressure controls. Many however reported adverse effects. Dose-related side effects appeared to occur commonly in patients given metoprolol and this could have lead to reduced compliance and hence inadequate blood pressure control. This could be due to reduced ability to metabolise metoprolol that could have occurred with some patients due to debrisoquine hydroxylase genetic polymorphism. Further work involving phenotyping and genotyping for the polymorphism may provide insights into this problem.

CHAPTER ONE

INTRODUCTION

1. INTRODUCTION

Hypertension is a major public health problem because of its consequences. It is an established risk factor for stroke, myocardial infarction, and premature cardiovascular death (Hennekens, 1998). As a risk factor for cardiovascular disease, hypertension almost competes with elevated plasma cholesterol for first place (Kaplan, 1983; Mansour et al, 1997). Thus although the facts about it are common knowledge, the consequences of hypertension bear repeating (McCarthy, 1997). Hypertension is widespread and is a major risk factor in myocardial infarctions. It is also the chief cause of stroke in people under age 65 and only diabetes is more instrumental than hypertension in causing end-stage renal failure.

The treatment of hypertension has been shown to also protect against stroke. On a population basis, it has been estimated that a reduction in blood pressure of 2 mmHg would result in a 15% reduction in risk of stroke and transient ischaemic attack and a 6% reduction in risk of coronary heart disease (Kothan et al, 1988). Stamler et al (1993) reviewed prospective population studies on blood pressure and cardiovascular risks. They concluded that systolic blood pressure and diastolic blood pressure had a continuous, graded, strong, independent and etiologically significant

relationship to a variety of outcome variables, including coronary heart disease, stroke, cardiac abnormality and mortality. Data from the Framingham Heart study (Kannel et al, 1971) showed that those with borderline isolated systolic blood pressure (SBP : 140-159 mmHg, DBP : ≤ 90 mmHg) were at high risk of developing hypertension or major morbid or fatal events than people with normal blood pressure. They found that 80% of men and women with borderline hypertension developed definite hypertension after 20 years and experienced excessive long-term risk of cardiovascular disease and death. For the middle aged and older persons systolic blood pressure relates more strongly to risk than diastolic blood pressure (Potter and High, 1990). A pilot study of systolic hypertension in the elderly (SHEP) also concluded that the prevalence of isolated systolic hypertension (SBP ≥ 160 mmHg and DBP ≤ 90 mmHg) increased from about 8% among peoples in their sixties to 22% by the age of 80 (SHEP Cooperative Research Group, 1991).

As evidence shows that hypertension increases with age, the problem of hypertension will increase in importance since the number of individuals over 60 years is expected to increase steadily in the next few decades to levels approaching one fourth of the total population. More individuals are expected to suffer from hypertension (Chobanian, 1983). Cross sectional and longitudinal studies have demonstrated a rise in blood pressure with age in industrialized societies. Systolic blood pressure increases in an almost linear fashion until the

age of 80 years whereas diastolic blood pressure increases till the age of 60 years and later plateaus and then falls. In the National Health and Nutrition Examination Survey (NHANES), the prevalence and severity of hypertension (SBP \geq 160 mmHg and/or DBP \geq 95 mmHg) increased with age. Hypertension occurred in over 40% of those aged 65 to 74 years old. Similar prevalence rates were reported in the United Kingdom, based on blood pressure measurements on a single occasion (Burt et al,1995).

The rise in blood pressure with age is also influenced by the racial origin. Blacks tend to have greater increase than whites and women are more prone compared to men. Blood pressure levels are also correlated among family members. A number of factors possibly contribute to this and they include the common genetic background and the shared environment or lifestyle habits. Prolonged effect of a particular life style and exposure to environmental factors for instance has been speculated to affect the blood pressure (Potter,1994; Stamler et al,1991). Thus hypertension appears to be a complex trait that does not follow the classical Mendelian rules of inheritance attributable to a single gene locus. The currently documented exceptions are a few rare forms of hypertension, such as those related to a single mutation involving a chimeric 11-B-hydroxylase/aldosterone synthase gene. Hypertension appears to be a polygenic and multifactorial disorder in which the interaction of several genes with each other and with the environment is important. Potential candidate

genes suggested by recent experimental data include those that affect various components of the renin-angiotensin-aldosterone system, the kallikrein-kinin system and the sympathetic nervous system.

Due to its complexity, direct consequences and prevalence, the prevention and treatment of hypertension therefore represent a major public health challenge.

Concerted efforts are required and have been shown to bear fruits.

Hypertension prevalence rates in the United States are on the decline, perhaps thanks to the efforts directed toward primary prevention. In the National Health and Nutrition Examination Survey (Burt et al, 1995). The prevalence of hypertension among US adults was 20.4%, compared to 31.8% in NHANES II (1976-80) and 36.3% in NHANES I (1960-62). From NHANES II until NHANES III, hypertension control rates also improved from 10% to 29% and cardiovascular disease mortality rates have improved dramatically. However hypertension control rates appear to be declining. NHANES III Phase 2, completed in the early 1990s, showed control rates slipping from 29% in NHANES III to 27%. (Burt et al, 1995). We are beginning to move in the wrong direction.

Thus the following continue to be among the challenges:

- 1) to prevent the rise of blood pressure with age,

- 2) to decrease the existing prevalence of hypertension,
- 3) to increase hypertension awareness and detection,
- 4) to improve control of hypertension,
- 5) to reduce other cardiovascular risks,
- 6) to increase recognition of the importance of controlled isolated systolic hypertension,
- 7) to improve recognition of the importance of high-normal blood pressure,
- 8) to reduce ethnic, socioeconomic and regional variation in hypertension,
- 9) to improve opportunities for treatment and to enhance community programs.

For the treatment of high blood pressure, many antihypertensive drugs are available. The choice of an appropriate antihypertensive is crucial and therefore needs to be considered carefully. The clinician must consider a number of factors especially in relation to the frequency of drug administration and the side effects that may arise from the medications as these may affect compliance (Rosenthal et al, 1996; Kesaniemi et al, 1991). The treatment goal is to make optimal use of antihypertensive drug therapy while encouraging patients to implement lifestyle changes such as weight loss, sodium restriction, decreased alcohol intake, and increased exercise (Hennekens, 1998). Pharmacologic therapy of mild-to-moderate hypertension can significantly reduce the incidence of stroke, coronary artery disease, vascular mortality and total mortality.

There are a number of therapeutic options for the treatment of hypertension and subgroup analysis of studies have shown the significant role of age, race and gender in the treatment process. Results from the Systolic Hypertension in the Elderly Programme, SHEP (SHEP Cooperative Research Group, 1991), the Swedish Trial in Old Patients with Hypertension, STOP-HPT (Dahlof et al, 1991), The Medical Research Council Trial of treatment of hypertension in older adults, MRC Trial (MRC Working Party, 1992) and the Treatment of Mild Hypertension Study, TOMHS (TOMHS Research Group, 1993) are examples. All the studies

used placebo-controlled and they have evaluated systolic and/or diastolic blood pressure. Active drug treatment with diuretics and beta blockers were used in the SHEP, STOP and MRC trials, whereas in TOMHS study, they compared the effectiveness of lowering stage 1 diastolic blood pressure using 5 different antihypertensive drugs with lifestyle modification versus placebo with lifestyle modification alone. Again these studies strongly supported the use of drug therapy for hypertensive patients including the elderly men and women. In most of the studies, both fatal and non-fatal stroke and coronary heart disease were reduced. In the STOP study for example, total mortality was reduced 47% by drug treatment.

Grimm (1996) from the University of Minnesota proposed that the cardiovascular risk was reduced both in men and women, regardless of the drugs used. This was based on a variety of critical cardiovascular endpoint measurements evaluated over a four years period in TOMHS study. These studies confirmed that the risk of cardiovascular event decreased as mean blood pressure decreased. In relation to age, both younger (≤ 60 years) and older (≥ 60 years) patients responded to antihypertensive treatment (TOMHS, 1993). Some studies including SHEP also showed that systolic pressure might be a better predictor of stroke and other cardiovascular events than the diastolic blood pressure in the elderly (SHEP Cooperative Research Group, 1991).

Therefore, lowering the systolic blood pressure is clearly important to reduce the risk of these events in the elderly.

Similar results were seen in MRC trial where 4000 men and women aged 65 to 74 years were enrolled. They were treated with diuretics, beta blockers or placebo. Patients treated with diuretics experienced a 31% reduction in strokes, 44% in coronary events and 35% in cardiovascular events. In this study, more than 49% of the patients enrolled had isolated systolic blood pressure (SBP ≥ 160 mmHg) and they benefited from the treatment of hypertension (MRC Working Party, 1992). Other trials such as the Systolic Hypertension-Europe (Sys-Eur) and Shanghai Trial of Nifedipine in the elderly (STONE) trials also showed benefits of treatment in the elderly, either of isolated systolic or both systolic and diastolic hypertension (Staessen et al, 1997; Gong et al, 1996). Overall, there is enough evidence to show that treatment of hypertension can reduce cardiovascular morbidity and mortality.

Experts have conflicting views on the choice of initial pharmacological therapy for hypertension however (American Heart and Lung Association Committee, 1993; Guidelines Sub-Committee, 1993; Carruthers et al, 1993; Jackson et al, 1993; Hypertension Guidelines Committee, 1991). However, approximately half the published guidelines consider that diuretics and beta-blockers are the only drugs that have been shown to reduce cardiovascular morbidity and mortality in

long-term outcome trials and recommend that they should be preferred for initial drug therapy.

A physician guideline for the prevention and treatment of high blood pressure was recently released by the National Heart, Lung and Blood Institute (NHLBI). This is known as The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). JNC VI recommends that diuretics and beta blockers be the first line treatment in patients with uncomplicated hypertension (American Heart and Lung Association Committee, 1997).

1.1 Beta blockers as an antihypertensive agents.

Many beta blockers are now available and in general they are equally effective.

There are, however, differences between them which may affect choice in treating individual patients. Beta blockers can be found either with or without intrinsic sympathomimetic activity (ISA). ISA represents the capacity of beta blockers to stimulate as well as to block adrenergic receptors. They tend to cause less bradycardia than the other beta blockers and may also cause less coldness of the extremities. Each of the above categories can be further divided into selective and non-selective beta blockers. Examples of the selective beta blocker which do not have ISA include metoprolol, atenolol, bisoprolol and betaxolol. The first two drugs are widely used for various indications including hypertension and ischaemic heart disease.

Some beta blockers are lipid soluble and some are water soluble. Atenolol, celiprolol, nadolol and sotalol are the most water soluble; they are less likely to enter the brain and may therefore cause less sleep disturbances and nightmares. In contrast, metoprolol which is lipid soluble, can freely cross the blood brain barrier.

Metoprolol is a selective B1-adrenoceptor antagonist with a predominant effect on the cardiac B1 receptors. Like other beta blockers, it has multiple actions to lower the blood pressure. It:

- a) blocks the cardiac B1 receptors and therefore it slows the heart rate at rest and after exercise via negative chronotropic affect. It also reduces the force of contraction, resulting in lowering of the cardiac output through its negative inotropic effect.**
- b) reduces the central sympathetic discharge to decrease the peripheral vascular resistance; and**
- c) suppresses the renal secretion of renin (mediated by B1) causing inhibition of the renin-angiotensin-aldosterone system.**

In the treatment of ischaemic heart disease, beta blockers reduce the impact of beta-adrenergic stimulation of the heart. It therefore reduces the cardiac work load and myocardial oxygen consumption. It also has anti arrhythmic effect and recently it has been proposed as one of the drugs of choice in the treatment of heart failure. The exact mechanism in heart failure is unknown but several possibilities have been proposed including upregulation of B receptors and increase receptor density, providing anti arrhythmic activity or protection against cardiotoxic effects of catecholamines.

Metoprolol is a competitive B₁-selective adrenergic antagonist, similar to atenolol. In contrast to pindolol, metoprolol does not have intrinsic sympathomimetic activity and does not exhibit membrane stabilizing activities as do both pindolol and propanolol. Metoprolol is more lipid soluble than atenolol, but less than propanolol and betaxolol. This affects its route of elimination and, theoretically, its potential for CNS side effects. Metoprolol also has the shortest half-life of the cardioselective B blockers.

Metoprolol competes with adrenergic neurotransmitters (eg. Catecholamines) for binding at sympathetic receptor sites. At lower doses metoprolol selectively blocks B-adrenergic receptors in the heart and vascular smooth muscle. As a result, it reduces both the resting and exercise heart rate and cardiac output together with the reduction in systolic and diastolic blood pressure. Selectivity for the B₁-receptor is lost at higher doses (≥ 400 mg/day) and it can also competitively block B-adrenergic receptors in the bronchial and vascular smooth muscles, causing bronchospasm.

Other than the use for the treatment of hypertension and ischaemic heart disease, metoprolol also has been used in the management of hereditary and familial essential tremor.

Metoprolol is rapidly and almost completely absorbed from the gut, but only 50% of an oral dose reaches the systemic circulation as unchanged drug because of first-pass metabolism in the liver. Hypotensive effects begin within 60 minutes of an oral dose of the immediate-release product. The maximal therapeutic effect occurs within the first week of treatment.

Metoprolol is widely distributed throughout the body, crosses the blood brain barrier and the placenta; and is concentrated in the breast milk. Even though it is not extensively bound to plasma proteins, the hypotensive effects can last up to one month after discontinuation of the drug, possibly because of extensive tissue binding.

Metabolism of metoprolol occurs primarily in the liver and both its alpha-hydroxylation and O-demethylation are mediated by debrisoquine-hydroxylase (Huang et al, 1999). Debrisoquine hydroxylase (CYP2D6) is highly polymorphic with large interethnic variations. Up to 10% of Whites are enzyme-deficient and are termed poor metabolisers (PM). Most are homozygous for CYP2D6*4, a mutant caused by an aberrant 3' splice recognition site. Another allele causing the PM phenotype in Whites is CYP2D6*3, a mutant caused by a single base deletion in exon 5. These alleles were relatively common in Whites but were absent or rare in Asians (Bertilsson et al, 1992; Lee et al, 1994; Johansson et al, 1994; Dahl et al, 1995). Compared to Whites, MR among Chinese extensive metabolizers (EMs) is shifted toward higher values. An

enrichment occurred in the log MR values between 0.2 to 1.0, indicating lower average activity (Lee and Jayaseelan, 1995). The mechanism is mutations that caused reduced enzyme activity. As an example, CYP2D6*10 was common in Asia but not among Whites (Johansson et al, 1994; Dahl et al, 1995; Armstrong et al, 1994). This allele has a mutation in C188 → T in exon 1 that caused reduced enzyme activity. The C188 → T polymorphism resulted in higher metoprolol plasma concentrations and lower urinary metoprolol metabolite levels in Chinese subjects and this finding suggests that a lower dose of metoprolol may be used in these subjects (Huang et al, 1999).

Metoprolol is generally well tolerated. Its adverse effects are generally mild and temporary usually occurring at the onset of therapy and diminishing over time. As most of its adverse reactions are extensions of its therapeutic affect and could thus be due to excessive plasma concentrations, its use among our local population may therefore be associated with a different spectrum of adverse effects due to the difference in the genetic polymorphism of CYP2D6 in the local population. Thus although its use is well studied in Western populations, direct extrapolation can be dangerous. Among the recognized side effects of metoprolol include:-

- 1) Sinus bradycardia.
- 2) Hypotension.

- 3) Congestive cardiac failure especially in patients with preexisting left ventricular dysfunction.
- 4) CNS side effects including dizziness, fatigue, mental depression and in some cases vivid dreams.
- 5) GIT side effects including diarrhea, nausea and vomiting.
- 6) Bronchospasm and dyspnoea that are more likely to occur if the dose is more than 400 mg/day as the beta selectivity of the drug is lost.
- 7) Hypoglycaemia and hyperglycaemia.
- 8) Hematological adverse reactions such as agranulocytosis.
- 9) Hypertriglyceridemia and decrease plasma HDLs during therapy.
- 10) Myalgia and musculoskeletal pain.
- 11) Elevated hepatic enzymes.
- 12) Sexual dysfunction, impotence and decrease libido.
- 13) Dermatological problems : pruritus, skin hyperpigmentation reversible alopecia, xerosis and exfoliative dermatitis.

Although metoprolol is generally well tolerated, it should be used cautiously in certain condition especially in the patient who has an underlying cardiac disease and in thyrotoxic patients as abrupt discontinuation of the drug can precipitate myocardial ischaemia, infarction, ventricular arrhythmias or severe hypertension and thyroid storm respectively. This drug is also contraindicated in severe bradycardia or advanced AV block, in the patients with cardiogenic

shock or systolic congestive heart failure, particularly in those with severe compromised left ventricular dysfunction. It should also not be used as a monotherapy in patients with pheochromocytoma. Metoprolol should also be used cautiously in diabetic and bronchial asthmatic patients.

In summary, hypertension is common but it can cause significant morbidity and mortality if not properly recognized and treated. On the other hand the treatment of hypertension is not without risk as it may cause unnecessary side effect which can affect the patient's quality of life. The use of drugs like metoprolol which undergoes metabolism via an enzyme that is polymorphic may pose special problems. A balance must therefore be sought to ensure that the patients are treated adequately and remained on the treatment for the rest of their natural lives. Starting antihypertensive therapy alone is not sufficient. Patients have to remain on the drugs until the ends of their natural lives and it is therefore disheartening that nearly 86% of new antihypertensive drug therapy patients interrupted or discontinued purchasing any form of antihypertensive medications during the first year of a study (McCombs JS et al, 1994), thus negating its potential benefits. Inability to adequately metabolise metoprolol as it would occur with patients with mutated CYP2D6 gene may cause an increased incidence of adverse effects that may eventually translate into non compliance.

1.2 Health-related Quality Of Life (HRQOL).

The term quality of life has been widely used in a number of disciplines to express the idea of personal wellbeing in a framework which goes beyond the simple economic equation of wellbeing with income (Jacobs, 1997).

Christopher J. Bulpitt defined it as the degree of subjective well being attributable to or associated with lack of symptoms, psychological state and activities pursued (Bulpitt, 1997). Others defined it as multifactorial psychological construct consisting of the minimum of physical, psychological, social and behavioral aspects of well-being and function as perceived by the patient (Aaronson and Bullinger et al, 1991).

Health related quality of life is the beliefs and behaviors of daily life which are governed by the degree of good or ill health that an individual, group or population experiences (Irvine, 1996). Health status and functional status are other terms often used to denote HRQOL. In fact the above three objects are often used interchangeably to refer to the health domain which ranges from negatively valued aspects of life including death to the other end of the spectrum of positively valued aspects eg. role function of happiness (Guyatt et al, 1993).

Drossman et al. described a model of HRQOL which included disease related features (disease symptoms, complications of the disease or side effects of treatment) and non disease features (such as cognitive function, personality, social support network, cultural practices and religion) (Garret and Drossman, 1990). Typical domains of HRQOL assessments include well being, pain and discomfort, body image and sexuality, mobility and ability to perform activities, ability to work or attend school and engagement in personal relationships. Traditionally, HRQOL is described from the patient's point of view (group or population), because physicians and family under-estimate or introduce bias in the assessment of disease impact (Guyatt et al, 1993).

The potential applications of HRQOL assessment have been summarized by Fitzpatrick (Fitzpatrick et al,1992). These include identification of the problems and needs of individuals or groups of patients, assessment of standard of health care, enhancement of knowledge concerning the disease clinical course and measurement of treatment efficacy in clinical trials. Furthermore HRQOL assessment is critical for economic (cost effectiveness and cost utility) analyses.

Three general measures of quality of life have been widely employed:

1. Sickness Impact Profile (SIP).

2. Nottingham Health Profile (NHP).
3. Quality of Well-Being Scale (QWB).

Each of the category carries advantage and disadvantages. For example, the QWB scale was found to be less useful than the SIP or NHP for the following reasons:

- it always need and interviewer.
- it is lengthy and difficult to administer.
- the overall score is dominated by the symptom scores and
- a single symptom is rated as the most distressing.

Comparing the SIP and NHP, the SIP is likely to be more sensitive to changes than NHP. Furthermore it requires less patients to demonstrate a given difference between the two groups studied. Many researchers now are replacing the above three general or generic measures with the short-form 36-item (SF-36) instrument. However prove is still required that 36 questions can replace the 136 questions of the SIP without loss of sensitivity to change or the emergence of floor and ceiling effects (Bulpitt, 1997).

Table 1. General measures of the quality of life. The summaries of the characteristics of the instruments.

	SIP	NHP	QWB
Covers important area?	yes	yes	yes
In dept' enquires?	yes	no	yes
Number of item	136	45	varies
Can be self-administered?	yes	yes	no
Average time for completion (min)	35	10	45
Valid and repeatable	yes	yes	yes
Floor and ceiling effect	minor	major	minor

There are three main types of instrument which have been used to assess HRQOL and they include:

1. Global index.

- HRQOL is usually of secondary importance to the study or questions,
- Summarizes HRQOL at a glance,
- Provides little information as to the cause(s) of impairment.

2. Generic instrument.

- is more comprehensive than a global assessment,
- permits comparisons among populations interventions,
- may be insensitive to detect subtle but important specific changes in status.

3. Disease-specific instrument.

- is best suited to detect important changes within populations (with time or treatment),
- may not be available for a particular disease,
- may be too detailed to discriminate among similar disease.

The interpretation of quality of life data is therefore important for therapeutic decision making and policy planning. The measurement properties of the

quality of life indices and scales used in therapeutic trials affect their ability to detect meaningful treatment differences.

Whichever the instruments used, whether disease-specific or generic instruments, should be adequately validated prior to their application in clinical research or practice. Validation of new HRQOL instrument requires a comparison with a currently accepted reference measure (criterion validation) or a hypothetical prediction of its performance (construct validation). Both a Health Status Index (HSI) and a health profile should be obtained where a HSI is a summary score that encompasses all the quality of life data, whereas a health profiles are instruments that attempt to measure all important aspects of HRQOL for example, the Sickness Impact Profile. Their use will assist in avoiding the missing of important observations or focusing on inconsequential problems.

CHAPTER TWO

OBJECTIVES

2. OBJECTIVES.

1. To determine the incidence of adverse events in patients given metoprolol.
2. To determine factors that govern occurrences of adverse drug reaction. ie. demography data.
3. To determine whether patients who develop side effect to metoprolol suffer reduced quality of life.
4. To compare objectives number 1, 2 and 3 with patients treated with enalapril.

CHAPTER THREE

METHOD

3. METHODOLOGY.

The study was part of a larger study to investigate the relevance of CYP2D6 polymorphism in patients with cardiovascular disease and received appropriate approvals of the Ethical Committee at USM.

3.1 Patient selection.

Consecutive patients attending the specialist medical clinic at HUSM for the treatment of hypertension were recruited if they satisfied the following inclusion and exclusion criteria:

3.1.1 Inclusion criteria:

1. Willingness to sign a written-informed consent.
2. Diagnosed with hypertension and treated with metoprolol and/or enalapril.
3. Ability to understand the protocols of the study.
4. Willingness to participate in the study and to follow all prescribed instructions.